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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/970,649	10/05/2001	Monica Jonsson	003300-833	2032

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EXAMINER	
HUI, SAN MING R	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 09/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/970,649	JONSSON ET AL.	
	Examiner	Art Unit	
	San-ming Hui	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37,60-75 and 77-96* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37,60-75 and 77-96* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 27, 2005 has been entered.

The addition of claims 90-96 is acknowledged. Claims 1-37, 60-75, 77-96 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-37, 60-75, 77-89, and 91-92 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for PLGA, does not reasonably provide enablement for other release controlling shell of a biocompatible and biodegradable polymers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In the instant case, the specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re*

Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art

7) the predictability of the art, and

8) the breadth of the claims.

Applicant fails to set forth the criteria that defines "release controlling shell of a biocompatible and biodegradable polymers". Additionally, Applicant fails to provide information allowing the skilled artisan to ascertain these compounds without undue experimentation. In the instant case, only a limited number of "release controlling shell of a biocompatible and biodegradable polymers" examples are set forth, thereby failing to provide sufficient working examples. It is noted that these examples are neither exhaustive, nor define the class of compounds required. The claims are so broad that they read on any polymer known to man. Without sufficient guidance disclosed in the instant specification, one of skilled in the art would have to perform undue experimentation to assess each embodiment individually for physiological activity and

search for suitable polymer compounds in order to practice the full scope of the invention. The instant claims read on all "release controlling shell of a biocompatible and biodegradable polymers", necessitating an exhaustive search for the embodiments suitable to practice the claimed invention. Applicants fail to provide information sufficient to practice the claimed invention, absent undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-37, 60-75, 77-96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woiszwillo et al. (US Patent 5,981,719, references of record), Ekman et al. (US Patent 4,822,535, references of record) in view of Laakso et al. (Journal of Pharmaceutical Sciences, 1986;75(10):962-967, references of record) and Takada et al. (US Patent 5,622,657, references of record), and WO97/14408 ('408).

Woiszwillo et al. teaches a method of preparing biological active microparticles suitable for parenteral administration by mixing an aqueous solution of bioactive compounds, such as insulin, leuprolide, and bovine Serum Albumin, with the solution of polyethylene glycol. The microparticles are collected after heating to temperature between 37 - 70°C, centrifuging and washing (See col. 21, line 11-34; also col. 5, line 65 - col.7, line 49). Woiszwillo et al. also teaches the biological active substances as enzymes, recombinant proteins, polypeptide, carbonhydrate, such as insulin, leuprolide, and Bovine Serum Albumin (See col. 7, line 50 – col. 8, line 32). Woiszwillo et al. also teaches the concentration of the polymer as between 5-50% (see col. 11, line 48). Woiszwillo et al. also teaches the solution of preferred polymers, including polyethylene glycol, having molecular weight of 3,000 to 500,000 daltons can be added to the solution of the macromolecules in order to form a microparticles (See col. 12, lines 33-42). Woiszwillo et al. also teaches the way to optimizing the microparticles by altering the particle size and temperature (See col. 13, lines 30-36).

Ekman et al. teaches a method to encapsulate bioactive substance in order to form solid microparticles by employing a two-phase emulsion system (See abstract, also col. 9, line 13 – 26). Ekman et al. teaches the two-phase system suitable for the preparation of such microparticle as polyethylene glycol/soluble starch/water (See col. 2, line 11-12). Ekman et al. also teaches the drying steps may be accomplished by evaporation or ultrafiltration, in which evaporation would include heating or reduced pressure (e.g., freeze-drying) (See col. 3, line 1-8). Ekman et al. also teaches the polyethylene glycol as preferred polymer and its molecular weight as 100-2,000,000 Da (See col. 4, line 36).

The references do not expressly teach the method of preparing microparticles by employing the method of Woiszwillo et al. followed by that of Ekman et al. The references do not expressly teach the herein claimed characteristics (i.e., nitrogen content, particle size, and amyloprectin content) of starch employed. The references do not expressly teach the optional steps recited in claims 35-37. The references do not expressly teach the herein claimed temperature employed. The references do not expressly teach the herein claimed concentrations and molecular weight of polyethylene glycol. The references do not expressly teach the coating of the solid starch microsphere with PLGA polymer by air suspension technique.

Laakso et al. teaches polyacryl starch is suitable as carrier for passive target drug delivery since polyacryl starch is rapidly taken up by the reticuloendothelial system (RES) (see the abstract). Laakso et al. also teaches the nitrogen content of polyacryl starch can be affected by the amount of initiator employed (See the abstract and figure

2 in page 964). Laakso et al. teaches the degradation of polyacryl starch can be affected by the amount of initiator employed and the degree of derivatization of the starch (See particularly the abstract and page 966-967, Discussion Section).

Takada et al. teaches a prolonged release biological active microparticles which is coated by copolymers of poyllactic/glycolic acid (See col. 7, line 15-53). Takada et al. teaches such sustained release formulation is useful for various peptides and hormones (See col. 3, line 28 – col. 4, line 34).

'408 teaches a method to coat microparticles with PLGA using air suspension techniques to protect the easily degraded drug actives from degradation when exposed to organic solvents onto the starch microparticles (See for example, claim 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the herein claimed micro particles by employing the method of preparing microparticles by employing the method of Woiszwillo et al. followed by that of Ekman et al. It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the suitable starch compounds herein claimed in the method of preparing the herein claimed microparticles. It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the herein claimed temperature and particle size in the herein claimed method. It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the herein claimed materials for preparing the optional sustained release shell for the microparticle. It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the herein claimed

temperature as well as concentrations and molecular weight of polyethylene glycol in preparing the herein claimed microparticles. It would have been obvious to one of ordinary skill in the art the time the invention was made to employ a coating of PLGA polymer by air suspension technique.

One of ordinary skill in the art would have been motivated to prepare the herein claimed microparticles by employing the method of Woiszwillo et al. followed by that of Ekman et al. because Woiszwillo et al.'s method is to prepare a microparticle and then Ekman et al. would further encapsulate such microparticle to increasing the stability of the biological active substances.

One of ordinary skill in the art would have been motivated to employ the suitable starch compounds herein claimed in the method of preparing the herein claimed microparticles since the polyacryl starch is well-known as useful for passive targeting drug delivery. Optimizing the nitrogen content, molecular weight, the starch solution concentration, the weight ratio between the biological active substance and starch, the temperature employed, and particle size would be considered obvious as being within the purview of skilled artisan.

One of ordinary skill in the art would have been motivated to employ the herein claimed materials for preparing the optional sustained release shell for the microparticle since such materials are well-known to be useful as sustained release material for peptide medicine. Employing the herein claimed polymer as sustained release shell would have been reasonably expected to be similarly useful.

One of ordinary skill in the art would have been motivated to employ the herein claimed temperature as well as concentrations and molecular weight of polyethylene glycol in preparing the herein claimed microparticles. Optimization is seen to be within the purview of the skilled artisan, absent evidence to the contrary.

Finally, one of ordinary skill in the art would have been motivated to employ a coating of PLGA polymer onto the starch microparticle by air suspension technique. The sustained release coating of PLGA is employed by air suspension technique so that the biologically active such as proteins or peptides would be protected from environment detrimental to the biological actives.

Response to Arguments

Applicant's arguments filed April 27, 2005 averring Ekman not capable modifying the teachings of Woiszwillo in arriving the instant invention have been fully considered but they are not persuasive. Applicants' argues that Woiszwillo's method of preparing micropaticle without the need of water-in-oil emulsion. As discussed in the previous office action, the benefit of employing the method of Woiszwillo followed by that of Ekman would be the stability increase of the biological active substances. The microparticles prepared by Woiszwillo et al.'s method can be further encapsulated by Ekman et al.'s method. That is from a single phrase process moving to a two-phase process just as herein recited. In other words, both methods are not used at the same time. Furthermore, there is no teaching away to discourage one of ordinary skill in the art to modify Woiszwillo's system to Ekman's system of preparing microparticles.

Applicant's reasoning is apparently based on the fact that Ekman teaches a multiple phase emulsion wile Woiszwillo is teaching a single-phase system. Such arguments are not found persuasive as discussed above.

Applicant further argues that the Woiszwillo's system is a complete system that the cited prior art fails to provide motivation to further modify microparitcles, which are prepared by Woiszwillo's method, by coating with starch. Such arguments have been considered, but are not found persuasive. As the applicant realized, Woiszwillo teaches that various materials can further stabilize the microparticles. The advantage of further encapsulating the biologically actives with starch is taught in Laasko. Therefore, possessing the teachings of the cited prior art, one of ordinary skill in the art would have been motivated to further encapsulate the Woiszwillo's microparticles by starch using Ekman's method.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (571) 272-0626. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

San-ming Hui
Primary Examiner
Art Unit 1617